REMARKS

Claims 1-3 and 5-9 are pending in the instant specification. Applicants have amended claims 1, 2, 5 and 6. Support for the amendment to claim 1 can be found in step (a) of claim 1. Support for the amendment to claim 2 can be found, for example, on page 4, lines 15-19 of the instant specification. Support for the amendment to claim 5 can be found, for example, in claim 5 as filed. Applicants have canceled claims 13-17 and reserve the right to pursue these claims in a continuation application. No new matter is added.

Claim Objections

The Examiner has objected to claims 1 and 16 on page 3 of the Office Action. The Examiner objected to claim 1 because the Examiner asserted that the phrase "a simulated redox perturbation" should be "a stimulated redox state perturbation". Further, the Examiner objected to claim 16 asserting that the word "are" between "employed" and "in step (b)" should be deleted. Applicants have amended claim 1 to comply with the Examiner's suggestions. Applicants have canceled claim 16. Thus, Applicants submit that these objections are overcome.

Claim Rejections

35 U.S.C. §112, Second Paragraph

The Examiner has rejected claims 2, 5-6 and 13-14, on page 3 of the Office Action, under 35 U.S.C. §112, second paragraph for indefiniteness. The Examiner alleged that these claims do not particularly point out and distinctly claim the subject matter which the Applicants regard as the invention. Applicants have canceled claims 13-14, rendering the rejection moot as it regards these claims.

The Examiner asserted that claim 2 was indefinite for reciting "alteration in NADH ratio". The Examiner argued that it was unclear what was intended by this phrase, whether it meant a change in the NADH concentration or change in comparison of NADH levels to NAD^+. Applicants have amended claim 2 to specify that the ratio is a NAD^+/NADH ratio. Applicants submit that a person having ordinary skill in the art would have recognized that this was the ratio referred to by NADH ratio.

The Examiner also asserted that claims 5 and 13 are indefinite for reciting "where the screening is performed in the presence of decreased oxygen tension". The Examiner argued that it is unclear what the oxygen is decreased in relation to. Applicants have amended claim 5 to stipulate that the oxygen tension is decreased in relation to room air. Applicants have canceled claim 13.

The Examiner also asserted that claim 6 was indefinite for reciting "the method of claim 5 where at least one protein employed in the determination is associated with a physiological process or a pathophysiological process." The Examiner argued that it is unclear what the determination refers to. Applicants have amended claim 6 to delete the term "determination" and make clear what the antecedent basis is.

The Examiner also asserted that claim 14 was indefinite for reciting "the method of claim 13 where at least one protein employed in the determination is associated with a physiological process or a pathophysiological process." Applicants have canceled claim 14.

In light of the above arguments and amendments, Applicants submit that claims 2 and 5-6 are definite and request that this rejection be withdrawn.

35 U.S.C. §112, First Paragraph

The Examiner has also rejected claims 1-3, 5-9 and 13-17, on page 5 of the Office Action under 35 U.S.C. §112, first paragraph for lack of written description (new matter). Applicants have canceled claims 13-17 rendering this rejection moot as it regards these claims. The Examiner alleged that the specification does not provide sufficient written description to support the phrase, "where the plurality of proteins are screened concurrently." Applicants respectfully disagree.

The instant specification teaches the screening of a plurality of proteins concurrently on page 22, lines 3-5. Mating pairs or transfectants in a yeast two hybrid system were exposed to continuous nitric oxide presence. Thus, the screening process of the two hybrid system was being performed concurrently for a plurality of proteins. Further, the specification references the methods of Uetz *et al.* Nature 403:623-7 (2000) for use in a yeast two-hybrid system. Uetz *et al.* teaches the screening of 6,000 yeast transformants in an array concurrently. Thus, Applicants submit that there is sufficient written description for the above limitation to claims 1-3 and 5-9 and request that this rejection be withdrawn

The Examiner has also rejected claims 13-17, on page 6 of the Office Action under 35 U.S.C. §112, first paragraph for lack of written description (new matter). Applicants have canceled claims 13-17 rendering this rejection moot as it regards these claims.

35 U.S.C. §102(b)

The Examiner has rejected claims 1-2, 5-6, 9 and 13-14, on page 8 of the Office Action, under 35 U.S.C. § 102(b) for being anticipated by Tucci *et al.* Journal of Endocrinology 157:13-24 (1998) ("Tucci"). Applicants have canceled claims 13-14 rendering this rejection moot as it regards these claims. The Examiner alleged that Tucci teaches establishing a protein interaction map according to the limitations of claims 1-2, 5-6, 9 and 13-14. Applicants respectfully disagree.

Tucci does not teach the mapping of protein interactions. The Examiner asserted that Tucci teaches a protein interaction map in Figure 2. The Examiner further alleged that Tucci teaches the use of radio labeled IGF-II protein to screen for protein-protein interactions between IGF-II and variants of IGFBP. However, these experiments measure the change in the expression of the various IGFBPs in normal oxygen and hypoxic conditions, not changes in interaction of these IGFBPs with IGF.[1]

Tucci teaches only the differential expression of various IGFBPs and not their differential interaction with IGF or any other protein. Hypoxia alters the expression of various IGF system peptides.[2] Levels of IGF-I, IGF-II, and IGFBPs 3, 4, 5, and 6 were measured.[3] While, radio-labeled IGF was used to measure the amount of IGFBP, no differential binding of IGF with IGFBP was shown. Radio-labeled IGF binding to IGFBP-4, 5, and 6, shown in Figure 2 was confirmed by Northern blot analysis or immunoblotting for these proteins.[4] No change in protein interactions were shown by the teachings of Tucci and thus no protein-protein interaction map is produced by the teachings of Tucci. The teachings of Tucci do not teach all of the limitations of claims 1-2, 5-6 and 9, and thus cannot anticipate them. Thus, Applicants request that this rejection be withdrawn.

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[1] *See* Tucci at the Title and Abstract.
[2] *Id.* at page 14, column 1, second full paragraph.
[3] *Id.* at pages 16-17.
[4] *Id.* at page 17.

The Examiner has also rejected claims 13-17, on page 10 of the Office Action, under 35 U.S.C. § 102(e) for being anticipated by Loehrlein *et al.* U.S. Patent Application Publication No. 2002/0160361 ("Loehrlein"). Applicants have canceled claims 13-17 rendering this rejection moot.

35 U.S.C. §103

The Examiner has rejected claims 1-3, 5-9 and 13-14, on page 12 of the Office Action, under 35 U.S.C. § 103 for being obvious over Tucci in light of Livingston *et al.* WO 00/74725 ("Livingston"). Applicants have canceled claims 13-14 rendering this rejection moot as it regards these claims. The Examiner alleged that Tucci teaches all of the limitations of the claims except a simulated redox state perturbation that is generated by the addition of superoxide, peroxide, hydrogen peroxide, alkoxides, sulfoxides, brominating species, chlorinating species, nitrosating molecules, nitric oxide, S-nitrosothiols, nitrating molecules, peroxynitrite, NO-generating molecules, glutathione-regulating enzymes, NADH-regulating enzymes and flavin regulating enzymes. The Examiner argued that Livingston corrects the deficiencies of Tucci by teaching these compounds. The Examiner further alleged that Livingston teaches the screening of differential protein-protein interactions in response to hypoxia. Applicants respectfully disagree.

As explained above, Tucci does not teach a method of screening for protein-protein interactions or making a map of protein-protein interactions as stipulated by claims 1-3 and 5-9. Tucci only teaches the screening of protein expression levels. Thus, Tucci does not teach or suggest all of the limitations of claims 1-3 and 5-9.

Livingston does not cure the deficiencies of Tucci. Livingston does not teach the screening of protein-protein interactions, but screening changes in protein expression in response to hypoxia.[5] Livingston only teaches the screening of protein-protein interactions, *e.g.* CH1 and HIF-1α in the presence of various compounds, to screen for compounds that would disrupt the interaction, thus finding a compound that modulates a transcriptional response to hypoxia in a

[5] *See* Livingston at *e.g.* page 1, lines 10-11 and page 3, lines 10-12.

cell.[6] Induction of hypoxia is not necessary for carrying out these assays,[7] as it is in the invention of claims 1-3 and 5-9. The methods of Livingston may be performed by using recombinant methods, like a mammalian two hybrid interaction.[8] Thus, Livingston does not teach screening for changes in protein expression in response to hypoxia.

Thus, the combination of Tucci and Livingston do not teach or suggest the limitations of claims 1-3 and 5-9. Thus, Applicants submit that claims 1-3 and 5-9 are not obvious over the combination of Tucci and Livingston and request that this rejection be withdrawn.

[6] *Id.* from page 13, line 23 to page 14, line 8.
[7] *Id.* at page 14, lines 7-8.
[8] *Id.* at page 14, lines 5-7.

CONCLUSION

A favorable action on the merits is respectfully requested. If further discussion of this case is deemed helpful, the Examiner is encouraged to contact the undersigned at the telephone number provided below, and is assured of full cooperation in progressing the instant claims to allowance.

Respectfully submitted,

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